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EXAMINER	
SANDALS,W	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/973,021	Applicant(s) rsen, Mouritsen, Hindersson, Duch, Sorensen, Dal
	Examiner WILLIAM SANDALS	Group Art Unit 1636

X Responsive to communication(s) filed on *Sep 29, 1999*

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-18, 20-26, 30, 31, 34-42, 48, 53, and 59-68* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *1-6, 8-18, 20-26, 30, 31, 34-42, 48, 53, and 59-68* is/are rejected.

X Claim(s) *7* is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____.

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *17*

X Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

DETAILED ACTION

Response to Arguments

1. Applicants have provided an abstract, and the objection is withdrawn.

2. Applicant's arguments in the personal interview regarding the rejection of claims 1, 2, 4, 5, 8-11, 15, 16, 20, 22-24, 30, 31, 35-37 and 39-42 under 35 USC 102 were persuasive, and the rejection is withdrawn.

3. Applicant's arguments and amendments to the specification in Paper No. 19, filed July 29, 1999 and in Paper No. 20, filed September 29, 1999 have overcome the rejection of claims 32-34 under 35 USC 112, first and second paragraph in the previous office action, and the rejection is withdrawn.

Claim Objections

4. Claim 38 depends from claim 19 which has been cancelled. Rewriting claim 38 as an independent claim or changing the dependency is required.

5. Claim 35 recites in lines 2 "nucleic acids". Previous amendments to the claims have changed the claims to read "ribonucleic acids". For clarity and consistency, the term "ribonucleic acids" would be preferred here.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 9, 20, 21, 34, 36 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 20, 34 and 36 recite the term "phenotypic trait", where the phenotypic trait in a cell is ascribable to the expressed ribonucleic acid(s) or peptide(s) affecting biological functions of the cell which have influence on the preselected phenotypic trait.

No nexus is provided in the claims or specification to inform one of ordinary skill in the art how to know when a phenotypic trait is ascribable to the expressed ribonucleic acid(s) or peptide(s) where they may affect biological functions of the cell. Lacking this guidance, the claim is vague and indefinite. Applicant's amendment of other claims to recite the term "cellular function" would correct this defect if applied to claims 20, 34 and 36.

9. Claims 9 and 37 appear to claim a Markush group without the proper use of the Markush format. Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being

"selected from the group consisting of A, B and C." See Ex parte Markush , 1925 C.D. 126 (Comm'r Pat. 1925).

10. Claim 34 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting an essential step, such omission does not set forth the method in clear and unambiguous terms. See MPEP § 2172.01. The omitted step is a correlation, or recapitulation step at the end of the claim which restates the preamble.

11. Claim 21 recites in line 7, "translocation of these to defined cellular compartments". The term "these" is not clear as to its antecedent basis in the claim. Inserting the antecedent terms here would correct this deficiency.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-6, 8-18, 20-24, 30, 31, 34-42, 48, 53 and 59-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al. in view of Woodring et al., US Pat No. 5,650,489, US Pat No. 5,770,434, Burke et al. and Wong et al.

The claims are drawn to a method for identification of biologically active nucleic acids or peptides or their cellular ligands by producing a pool of vectors wherein the vectors are produced

from: (a) synthetic totally random DNA sequences, (b) synthetic, partially random DNA sequences, (c) sequences of (a) or (b) coupled to sequences encoding purification tags, (d) sequences or (a), (b) or (c) coupled to a coding sequence of a protein, wherein the vectors of (a), (b), (c) or (d) are expressed in cells and produce an altered cellular function in the cell, and wherein the translated RNA or expressed peptide product are (e) sequenced or (f) used to directly isolate a ligand to the biologically active nucleic acid or peptide. The peptide may be glycosylated. The peptide may be fused to a protein, which may be a F(ab) or antibody molecule. The synthetic nucleic acids may be made by conventional random oligonucleotide synthesis. The random DNA sequences may be introduced into the vector by site directed PCR-mutagenesis, where the ends of the PCR product may be trimmed by 3'-5' exonuclease. The vectors may be transduced into the cells to produce a single transfectant vector in a single cell. The vector may be a viral vector which may be a retrovirus or vaccinia virus, where the retrovirus vector has heterologous ends at the insertion site of the random sequences, where the heterologous ends may contain two different promoters, and where a CMV promoter may replace the 5' LTR. The viral vector may be introduced into the cell by non-viral transfection methods. The vector may be amplified by PCR prior to the transfection step. The host cell may be a viral packaging cell which has been transfected with a vector expressing a single transcript consisting of gag-pol, a drug resistance gene and the env gene. The packaging cell may be a semi-packaging cell line which has been transfected with a minivirus vector. The host cell may be cotransfected with a tRNA suppressor gene. The biologically active peptide may contain a purification tag. The

random DNA sequences may be integrated into the coding sequence of a protein producing a fusion protein, where the protein may be a secreted protein, an intracellular protein or a membrane protein (e.g. a signal transducing protein), which may be an antibody which may be a part of a heavy and/or light chain of an antibody molecule. The partly random sequences may encode glycosylation sites or anchor residues, or signal sequences or leader sequences or recognition sequences, which may direct the fusion proteins to defined cellular compartments.

Kay et al. taught (see especially columns 3-6, 16-18, 22-24, and 28) a method for identification of biologically active nucleic acids or peptides or their cellular ligands by producing a pool of vectors wherein the vectors are produced from synthetic, partially random DNA sequences. These sequences may be coupled to sequences encoding purification tags, or coupled to a coding sequence of a protein, wherein the vectors are expressed in cells and produce a altered function in the cell, and wherein the translated RNA or expressed peptide product are sequenced or used to directly isolate a ligand to the biologically active nucleic acid or peptide. The peptide may be fused to a protein, which may be a F(ab) or antibody molecule.. The synthetic nucleic acids may be made by conventional random oligonucleotide synthesis. The partially random DNA sequences may be introduced into the vector by site directed PCR-mutagenesis. The vectors may be transduced into the cells to produce a single transfectant vector in a single cell. The vector may be a viral vector which may be a retrovirus or vaccinia virus, where the retrovirus vector has heterologous ends at the insertion site of the random sequences. The vector may be amplified by PCR prior to the transfection step. The host cell may be

cotransfected with a tRNA suppressor gene. The biologically active peptide may contain a purification tag. The random DNA sequences may be integrated into the coding sequence of a protein producing a fusion protein, where the protein may be a secreted protein, an intracellular protein or a membrane protein (e.g. a signal transducing protein), which may be an antibody which may be a part of a heavy and/or light chain of an antibody molecule.

Kay et al. did not teach that the synthetic nucleic acid were totally random, nor that the ends of the PCR product may be trimmed by 3'-5' exonuclease nor that the vectors may contain two different promoters, and where a CMV promoter may replace the 5' LTR. The viral vector may be introduced into the cell by non-viral transfection methods. Also not taught was that the host cell may be a viral packaging cell which has been transfected with a vector expressing a single transcript consisting of gag-pol, a drug resistance gene and the env gene. The packaging cell may be a semi-packaging cell line which has been transfected with a minivirus vector.

Woodring et al. taught (see especially the abstract and materials, the introduction and methods) the use of totally random synthetic nucleic acids to alter a cellular function in a cell by direct activity or by the ligand binding of the nucleic acid or its expressed RNA or peptide.

US Pat No. 5, 770,434 taught (see especially column 3) the use of synthetic nucleic acids coding for totally random peptide sequences which are expressed in host cells to identify those sequences which alter cellular function.

US Pat No. 5,650,489 taught (see especially columns 2-15) totally random synthetic nucleic acids which were used for selection of effector molecules (DNA, expressed RNA or expressed Peptides) and ligands molecules.

Burke et al. taught (see especially columns 1-6) that the viral vector in an expression library contained partially random DNA sequences which encoded leader sequences and anchor sequences for fusion proteins, where the sequences were glycosylated and also leader sequences which directed the fusion proteins to specific cellular compartments.

Wong et al. taught (see especially the abstract and introduction, materials and methods and the Figures) the well known use of a 3'-5' exonuclease to blunt end inserts for ligation into a vector, the inclusion of an antibiotic marker gene into a vector and the incorporation of a strong promoter such as the CMV promoter into a viral vector in order to produce an expression library where the vector encodes a detectable alteration in the phenotype of the host cell.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Kay et al. with Woodring et al., US Pat No. 5,650,489, US Pat No. 5,770,434, Burke et al. and Wong et al. to produce the instant claimed invention because Kay et al. taught the use of a library of partially random DNA sequences which would act as expressed tags for identification when linked to coding sequences for proteins of interest, or as leader sequences, anchors or sites for post-translational modification. Kay taught the use of viral vectors for the expression libraries, and the use of antibodies and antibody components as fusion proteins with random sequences as described above where the translated proteins and transcribed

RNA's were used to detect alterations in the phenotype of the host cell. Woodring et al. and US Pat No. 5,770,434 taught the use of totally random sequences to produce expressed RNA's and peptides which affect the cellular function of a cell, and using the totally random sequences in a method of identifying and isolating such sequences. Burke et al. taught the use of random sequences linked to sequences encoding proteins to produce fused leader sequences, "tags", and post-transcriptional and post-translational modifications of the fused polypeptides to identify vector induced alterations in the phenotype of the host cell. Wong et al. taught the modification of inserts in viral vectors to produce an expression library where the vector encodes a detectable alteration in the phenotype of the host cell.

One of ordinary skill in the art would have been motivated at the time of the instant invention to combine the teachings of Kay et al. with Woodring et al., US Pat No. 5,650,489, US Pat No. 5,770,434, Burke et al. and Wong et al. to produce the instant claimed invention because Kay et al. taught the use of a library of random DNA sequences which would act as expressed tags for identification when linked to coding sequences for proteins of interest, or as leader sequences, anchors or sites for post-translational modification. Kay taught the use of viral vectors for the expression libraries, and the use of antibodies and antibody components as fusion proteins with random sequences as described above where the translated proteins and transcribed RNA's were used to detect alterations in the phenotype of the host cell. Kay et al. states at column 4 lines 25-28 "[t]he present invention provides methods and compositions, i.e., libraries, for identifying proteins/polypeptides and/or peptides called TSARs (totally synthetic affinity

reagents) which bind to a ligand of choice". Woodring et al. and US Pat No. 5,770,434 taught the use of totally random synthetic DNA's in a method to select DNA's which effect a change in cellular function. US Pat No. 5,650,489 taught the use of random sequence of peptides to effect a change in cellular function. Burke et al. taught the desirable use of random DNA sequences linked to DNA sequences encoding proteins to produce fused leader sequences, "tags", and post-transcriptional and post-translational modifications of the fused polypeptides to identify vector induced alterations in the phenotype of the host cell. Wong et al. taught the modification of inserts in viral vectors to produce an expression library where the vector encodes a detectable alteration in the phenotype of the host cell. Since all of the references taught a key element of the instant claimed invention which is the detection of an altered phenotype in a host cell, it would have been obvious to combine these references to produce the instant claimed invention. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Kay et al. with Woodring et al., US Pat No. 5,650,489, US Pat No. 5,770,434, Burke et al. and Wong et al.

Response to Arguments

14. Applicants have argued in Paper No. 13, filed on February 1, 1999, that Burke et al. did not teach totally random DNA sequences. This is correct and the above paragraph has been appropriately amended. Burke et al. is cited to demonstrate the well known use of leader sequences and anchor sequences for fusion proteins, and where they demonstrated that these sequences may be glycosylated by the host cell.

15. Applicants have argued in Paper No. 13, filed on February 1, 1999 that motivation to combine the references was insufficient. Since Burke et al. was cited to provide evidence of the well known teachings of viral vector in an expression library which contained partially random DNA sequences which encoded leader sequences and anchor sequences for fusion proteins, where the sequences were glycosylated and also leader sequences which directed the fusion proteins to specific cellular compartments. Wong et al. was cited to provide evidence of the well known use of a 3'-5' exonuclease to blunt end inserts for ligation into a vector, the inclusion of an antibiotic marker gene into a vector and the incorporation of a strong promoter such as the CMV promoter into a viral vector in order to produce an expression library where the vector encodes a detectable alteration in the phenotype of the host cell. Kay et al. provided the basis for the rejection in its teachings of the use of random oligonucleotides which encoded and expressed small RNAs and peptides on the surface of cells for the purpose of identifying the functional aspects of the small RNAs and peptides. Burke et al. and Wong et al. merely provided evidence of teachings well known in the art. A nexus to the teachings of Kay et al. where they were all investigating a "key element" of the claimed invention is sufficient to provide motivation to combine the teachings to produce the instant claimed invention.

16. Applicants have argued in the Personal Interview of September 21, 1999 and in Paper No. 20, filed September 29, 1999 that Kay et al. taught that the synthetic random DNA sequences were large and therefore taught away from the small molecules of the instant claimed invention. The addition of the teachings of Woodring et al., US Pat No. 5,650,489, US Pat No. 5,770,434

are added to the previous rejection to demonstrate the obviousness of the use of totally random small synthetic nucleic acids to produce the instant claimed invention.

17. Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al. with Woodring et al., US Pat No. 5,650,489, US Pat No. 5,770,434, Burke et al. and Wong et al., as applied to claims 1-6, 8-18, 20-24, 30, 31, 34-42, 48, 53 and 59-68 above, and further in view of Stemmer et al.

The claims are as described above and are also drawn to the screening wherein T-cell epitopes bound to MHC molecules are present on the surface of transduced cells, which may be a phenotypic trait.

Stemmer et al. taught (see especially the abstract, the summary of the invention, column 10, lines 20-29, column 13, lines 21-31 and column 14, lines 27-32) the expression of random peptides which are T-cell epitopes, which are presented on MHC molecules on the surface of transduced host cells, which may be a phenotypic trait.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Kay et al. with Woodring et al., US Pat No. 5,650,489, US Pat No. 5,770,434, Burke et al. and Wong et al. with Stemmer et al. because Kay et al. taught the basis for the rejection in its teachings of the use of random oligonucleotides which encoded and expressed small RNAs and peptides on the surface of cells for the purpose of identifying the functional aspects of the small RNAs and peptides. Stemmer et al. were investigating the use of

random oligonucleotides which encoded and expressed small RNAs and peptides on the surface of cells for the purpose of identifying the functional aspects of the small RNAs and peptides, just as was Kay et al. Stemmer et al. states that "it would be advantageous to develop a method which allows for the production of large libraries of mutant DNA, RNA or proteins and the selection of particular mutants for a desired goal". Kay et al. states "the invention provides a rapid and easy way of producing a large library that results in a plurality of longer proteins, polypeptides and/or peptides that can efficiently be screened to identify those with novel and improved binding specificities, affinities and stabilities for a given ligand of choice". Thus it is clear that Kay et al. and Stemmer et al. were motivated to identify similar binding ligands which were made from random short DNA's encoding short peptides and polypeptides of interest, where Stemmer et al. were investigating a subset of the teachings of Kay et al. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Kay et al. with Woodring et al., US Pat No. 5,650,489, US Pat No. 5,770,434, Burke et al., Wong et al. and Stemmer et al.

Allowable Subject Matter

18. Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

19. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
December 1, 1999

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER